UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,101	04/04/2002	Sydney Brenner	5525-0044.10	9341

22918 7590 10/19/2004

PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,101	BRENNER, SYDNEY	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,13 and 14* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 April 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-6, 13, and 15 in the reply filed on 8/13/04 is acknowledged. Claims 5-12 and 15-20 have been cancelled.

2. The international search report and the IPER in the parent PCT application have been reviewed.

Drawings

3. The drawings are objected to because many of the figure numbers are cut off in the drawings or are difficult to read (see figure 1A, 2D, 3, 5A, 6A, 5, 6B, 8B, 9A, and 9B). Figure 7B is difficult to read, much of the illustrated electropherogram is a large black blur. In figure 10A there is some hand written markings in the upper left hand corner that are not clear. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified

and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

4. Claim 14 is objected to because of the following informalities: there are apparent typographical errors in line 1 of the claim (libbrary) and line 6 of the claim (memter) . Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4, 13, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claims 1-4, the claim defines a "polymorphic consensus sequence" as being a theoretical sequence obtained by aligning DNA and projecting restriction sites onto the sequence, yet the claim also describes nucleic acid fragments that are subregions of this consensus sequence. It is not clear what it means for an actual nucleic acid fragment to be a subregion of a theoretical sequence. Furthermore, the claim recites that the fragments (b) are "derived" from a non-polymorphic subregion, but it is not clear what it means for a fragment to be "derived" from a subregion of a theoretical sequence. Also, the definition of the polymorphic consensus sequence is not clear because it is not clear what it means to align "pooled DNA"

because "pooled DNA" appears to refer to actual DNA molecules yet the "aligning" step appears to be a step of data manipulation. Further, it is unknown what is meant by "projecting" restriction sites onto said sequence. The claims are entirely unclear as to how the definition of the theoretical consensus sequence is structurally limiting to the claimed library as these are process limitations that define how the product could be identified, but it is not clear what they mean with regard to the structure of the claimed product.

In claim 1, line 5, it is unclear if the phrase "derived from said pooled DNA" modifies the previously mentioned portion of a polymorphic subregion or the previously mentioned consensus sequence.

Furthermore, it is not clear what it means for the library to be "enriched" for a particular type of fragments relative to one another. It is not clear if that means, for example, that there are more of fragments of type (a) than type (b) in a sample or if a product which has less fragments of type(a) than type (b) could be within the scope of this "enrichment." An example of the latter would be, for example, a library that begins with far more fragments of type (b) than type (a) and some of the fragments of type (b) are removed, but still there remain more fragments of type (b) than type (a). Is this type of library "enriched" for type (a) relative to type (b)? The specification does not define this enrichment, and therefore the library encompassed within the scope of these claims is not clear.

In claim 13, the phrase "the same locus" in line 5 lacks proper antecedent basis in the claims as the claims do not previously refer to a locus and it is not clear what potential loci are present nor which locus is "the same locus." This claim is also unclear over the meaning of "having one or more restriction site polymorphisms" because it is not clear what it actually

means to "have" the polymorphism. That is, must a nucleic acid having an allele be present which prevents a restriction enzyme from cutting or if the allele which the enzyme cuts is present is this sufficient, or does the claim require nucleic acids having both alleles to be present? Further, in this claim, the phrase "the number of such members forming a proper subset" is entirely unclear because it is not clear what is meant by a "proper subset" or how this recitation is limiting to the claim.

In claim 14, the phrase "the same locus" in line 5 lacks proper antecedent basis in the claims as the claims do not previously refer to a locus and it is not clear what potential loci are present nor which locus is "the same locus." This claim is also unclear over the meaning of "having one or more restriction site polymorphisms" because it is not clear what it actually means to "have" the polymorphism. That is, must a nucleic acid having an allele be present which prevents a restriction enzyme from cutting or if the allele which the enzyme cuts is present is this sufficient, or does the claim require nucleic acids having both alleles to be present?

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 13, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ausubel *et al.*, WO 95/25538.

Ausubel *et al.* teach a nucleic acid reference library comprising a heterogenous mixture of nucleic acid fragments wherein each fragment

(a) is a portion of a polymorphic subregion of a polymorphic consensus sequence derived from said pooled DNA or (b) is derived from a non-polymorphic subregion,

each of said polymorphic subregions is bounded by first restriction sites and comprises an internal polymorphic restriction site which is different from said first site;

said polymorphic consensus sequence is the theoretical sequence obtained by (i) aligning said pooled DNA to provide maximum homology, and (ii) projecting each of said restriction sites onto said sequence; and

said library is enriched for fragments of type (a) relative to type (b).

Example XI taught by Ausubel *et al.* (beginning on page 59) teaches a method for cloning polymorphic restriction fragments. Namely, turning to figure 9 taught by Ausubel *et al.*, section 9D and 9E both provide a library which is enriched for fragments that are portions of polymorphic subregions of organism A compared to organism B. For example, in the library of nucleic acids in figure 9D, the fragment 5' which was present in both organism A and organism B is not present in the library since enrichment steps were applied that resulted in the exclusion of fragments that were common to both organisms. In the library of nucleic acids in figure 9E is entirely comprised of sequences that comprise a portion of a subregion of a polymorphic consensus sequence and are bounded by first restriction sites.

With regard to the limitations within claim 1 that require that the sequences are portions of a "polymorphic consensus sequence" that is a theoretical sequence, as noted in the previous rejections under 112 2nd paragraph, it is not clear how an actual nucleic acid sequence can be a

portion of a theoretical sequence. Further, and to the point for this rejection, it is not clear what structural limitations are added to the claim by requiring that the fragments within the claimed library are fragments of a theoretical sequence obtained by aligning pooled and "projecting" a restriction site onto a sequence.

With regard to claim 2, the fragments in the libraries taught by Ausubel *et al.* comprise oligonucleotide tags (referred to therein as adaptors) and different fragments are linked to different oligonucleotide tags (in Figure 9D, for example).

With regard to claim 3, Ausubel *et al.* teach cloning the isolated sequences, a step which inherently comprises putting the fragments of the library into a repicable vector (p. 60, lines21-22).

With regard to 13, Ausubel *et al.* teach a heterogeneous mixture of restriction fragments of a first restriction endonuclease wherein said restriction fragments contain members have one or more restriction site polymorphisms with respect to a second restriction endonuclease. These members form a subset of the total number of restriction fragments (see the library in figure 9D which has fragments from restriction enzyme A that are polymorphic with respect to restriction enzyme B, and the library is a mixture of fragments from organism A and organism B).

With regard to claim 14, Ausubel *et al.* teach a heterogeneous mixture of restriction fragments of a first restriction endonuclease wherein the fragments include at least one member having one or more restriction site polymorphisms with respect to a second restriction endonuclease and at least one member without said polymorphism. Again see the library of figure 9D wherein fragments 6 has the polymorphism but fragment 1-2 was cut with enzyme B.

Therefore, the teachings of Ausubel *et al.* anticipate the rejected claims.

9. Claims 1, 13, and 14 are rejected under 35 U.S.C. 102(b) and 102(a) as being anticipated by Pierard *et al.* (Journal of Clinical Microbiology, Nov. 1998, p. 3317-3322), as evidenced by GanBank AF043627.

This application claims priority to two provisional applications. A review of these applications by the examiner did not identify support for the instantly claimed invention in the provisional applications. For example, no descriptive support for the limitations of claims 1-4 which refer to or describe the polymorphic consensus sequence was located. With regard to claims 13 and 14, no basis was identified for the "forming a proper subset" limitation in claim 13 or the limitations which refer fragments of "the same locus" in both claims. Therefore, the priority date of the instantly rejected claims is determined to be the instant filing date and the reference is available under 102(b). Nonetheless, the reference is also available under 102(a) as of even the earliest possible filing date. In the event that applicant is able to establish priority for the instantly claimed invention to one or both of the provisional applications the rejection under 102(b) will be withdrawn but the rejection under 102(a) will remain.

With regard to claim 1, Pierard *et al.* teach a nucleic acid library comprising a heterogeneous mixture of nucleic acid fragments wherein each fragment is a portion of a polymorphic subregion of a polymorphic consensus sequence and the polymorphic subregion is bounded by first restriction sites and comprises an internal polymorphic restriction site.

Pierard *et al.* amplify a portion of the E. coli genomes that comprises polymorphic restriction sites. The amplified fragments are from a sample of E. coli which inherenltly comprises DNA from at least two sources which are more than one cell. The fragments in the amplified library taught by Pierard *et al.* are a portion of a polymorphic subregion of a consensus

sequence that are bounded by first restriction sites and comprise an internal polymorphic restriction site. For example, Pierard *et al.* amplify sample using primers VT2-e and VT2-f in order to amplify nucleic acid that comprises polymorphic HaeIII and PvuII sites (see Table 2 and p. 3318). These primers amplify a portion of DNA that comprises the following sequence (numbering and sequence as in GenBank AF043627, enclosed herein and referred to in Pierard *et al.* at page 3318)

1059-aa tactttatgg gaaagtaata ccgcagctgc ttttctgaat cgcagggctc actctttaaa tacatccgga gaataacggg agttaaatat gaagaagata tttgtagcgg ctttatttgc ttttgtttct gttaatgcaa tggcagctga ttgtgcaaaa ggtaaaattg agttctctaa gtataatgag aatgatacat tcacagtaaa agtggccggg aaagagtact ggactaaccg ctggaatctg caaccgctac tgcaaagcgc acagttaaca ggaatgacgg taacaatcaa atcaaatacc tgtgcgtcag gttcaggatt tgctgaagtg cagttta-1407

This amplified portion comprises a polymorphic restriction site PvuII, for example beginning at nucleotide 1204 above which is bounded by first restriction sites TseI beginning at nucleotide 1176 on the 5' end and Restriction site EaeI beginning at nucleotide 1273 on the 3' end of the polymorphic restriction site. The library of amplified fragments is entirely composed of portions of polymorphic subregions since only polymorphic subregions are amplified.

With regard to claim 13, Pierard *et al.* further teach cutting the amplified fragments subsequent to amplification. Since these fragments are polymorphic for more than one restriction site, cutting with a first enzyme will produce a population of fragments that are polymorphic for also a second restriction endonuclease. With regard to claim 14, some of the samples contain different strains of E. coli which would then contain fragments that have both

alleles of some of the restriction enzymes (see table 3, for example a sample that contains VT2vh-a and VT2d-Ount).

Therefore the teachings of Pierard *et al.* anticipate the rejected claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ausubel *et al.* in view of Brenner (US 5604097).

Ausubel *et al.* teach a nucleic acid reference library comprising a heterogenous mixture of nucleic acid fragments wherein each fragment

(a) is a portion of a polymorphic subregion of a polymorphic consensus sequence derived from said pooled DNA or (b) is derived from a non-polymorphic subregion,

each of said polymorphic subregions is bounded by first restriction sites and comprises an internal polymorphic restriction site which is different from said first site;

said polymorphic consensus sequence is the theoretical sequence obtained by (i) aligning said pooled DNA to provide maximum homology, and (ii) projecting each of said restriction sites onto said sequence; and

said library is enriched for fragments of type (a) relative to type (b).

Example XI taught by Ausubel *et al.* (beginning on page 59) teaches a method for cloning polymorphic restriction fragments. Namely, turning to figure 9 taught by Ausubel *et al.*,

section 9D and 9E both provide a library which is enriched for fragments that are portions of polymorphic subregions of organism A compared to organism B. For example, in the library of nucleic acids in figure 9D, the fragment 5' which was present in both organism A and organism B is not present in the library since enrichment steps were applied that resulted in the exclusion of fragments that were common to both organisms. In the library of nucleic acids in figure 9E is entirely comprised of sequences that comprise a portion of a subregion of a polymorphic consensus sequence and are bounded by first restriction sites.

With regard to the limitations within claim 1 that require that the sequences are portions of a "polymorphic consensus sequence" that is a theoretical sequence, as noted in the previous rejections under 112 2nd paragraph, it is not clear how an actual nucleic acid sequence can be a portion of a theoretical sequence. Further, and to the point for this rejection, it is not clear what structural limitations are added to the claim by requiring that the fragments within the claimed library are fragments of a theoretical sequence obtained by aligning pooled and "projecting" a restriction site onto a sequence.

With regard to the limitations of claim 2, from which claim 4 depends, the fragments in the libraries taught by Ausubel *et al.* comprise oligonucleotide tags (referred to therein as adaptors) and different fragments are linked to different oligonucleotide tags (in Figure 9D, for example). Ausubel *et al.* do not teach libraries wherein the tags comprise sequences as described within claim 4.

Brennan teaches oligonucleotide tags comprised of subunits from a minimally cross-hybridizing set as described in claim 4 (see Col. 6-9, for example). Brennan teaches that these tags are useful to provide a system for tagging and sorting many thousands of fragments for

simultaneous analysis and/or sequencing (Col. 3, lines 3-8). Brennan exemplifies the use of these tags for labeling restriction fragments (See example 2, Col. 24).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Ausubel *et al.* so as to have included the use of oligonucleotide tags such as those taught by Brennan. One would have been motivated to utilize the tags taught by Brennan in order to take advantage of the express benefits of the methods taught by Brennan for sorting and analyzing complex mixtures of nucleic acid sequences. Therefore in view of the teachings of the prior art, the instant invention is prima facie obvious.

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the

USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Examiner
Art Unit 1634

October 13, 2004